reotactic technique and the judicious determination of the radiation dose are key factors in decreasing the complication rate.

Because radiosurgery is a new technology, it is still considered a secondary choice to the resection of lesions of the brain. But its proven effect, noninvasive nature, and cost-effectiveness—it is usually done on an outpatient basis—will make this technique more and more a part of the treatment of brain lesions.

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REFERENCES

Friedman WA, Bova FJ: Linear accelerator radiosurgery for arteriovenous malformations. J Neurosurg 1992; 77:832-841

Loeffler JS, Alexander E 3d, Shea WM, et al: Radiosurgery as part of the initial management of patients with malignant gliomas. J Clin Oncol 1992; 10:1379-1385

Loeffler JS, Kooy HM, Wen PY, et al: The treatment of recurrent brain metastases with stereotactic radiosurgery. J Clin Oncol 1990; 8:576-582

Lunsford LD, Kondziolka D, Flickinger JC, et al: Stereotactic radiosurgery for arteriovenous malformations of the brain. J Neurosurg 1991; 75:512-524

Ticlopidine Hydrochloride and Prevention of Stroke

TICLOPIDINE HYDROCHLORIDE is a novel platelet antiaggregant agent now available in the United States as an alternative to aspirin for the secondary prevention of stroke. Unlike aspirin, ticlopidine and other thienopyridine compounds have no effect on cyclooxygenase. Specific mechanisms of action remain under investigation, but likely involve the inhibition of adenosine diphosphate signal transduction at the platelet membrane. Ticlopidine provides greater efficacy than aspirin, but at the expense of more substantial adverse effects.

The Ticlopidine Aspirin Stroke Study directly compared these agents in subjects with recent transient ischemic stroke or mild ischemic stroke (cerebral or retinal) and found a 21% relative risk reduction in stroke (intention-to-treat analysis) with ticlopidine, 250 mg twice a day, versus aspirin, 650 mg twice a day. Benefits of ticlopidine use were shown in both sexes, with a three-year relative risk reduction in stroke of 27% for women and 19% for men. Notably, the advantage of ticlopidine use was greatest during the initial year: stroke recurrence was nearly halved compared with aspirin treatment.

Meta-analysis of all placebo-controlled aspirin trials before 1988 provides an estimated stroke risk reduction of 22% in subjects with a previous transient ischemic attack or minor stroke. These protective effects of aspirin can probably be generalized to women and to persons who have had a substantial stroke. The evidence for its efficacy in women is not extensive, however, and no large trials have evaluated the use of aspirin for preventing secondary stroke exclusively following a completed stroke. The Canadian American Ticlopidine Study, a placebo-controlled trial in subjects with recent thromboembolic stroke, showed a 33.5% stroke risk reduction during the first year in women and men receiving ticlopidine. Efficacy analysis also revealed a 30.2% risk reduction with ticlopidine use for combined stroke, myocardial infarct, and vascular death.

Most side effects of ticlopidine use—diarrhea, dyspepsia, rash—are minor, but lead to medication cessation in about one of five subjects. Serum cholesterol levels may increase slightly, but this occurs in patients with a reduced incidence of stroke, myocardial infarct, and vascular death. Although bleeding time is prolonged, serious hemorrhage is uncommon and gastrointestinal bleeding less common than with 1,300 mg per day of aspirin. The major adverse effect of ticlopidine use is a severe, reversible neutropenia (less than 450×10^3 neutrophils per liter) occurring in nearly 1% of patients, with onset virtually always during the first three months of therapy. Complete blood counts must be obtained every two weeks during the first three months of treatment. In the Ticlopidine Aspirin Stroke Study, the incidence of serious adverse effects did not differ between groups. Nevertheless, only reliable persons who understand the risks of ticlopidine should be considered treatment candidates.

The benefits of ticlopidine therapy are greatest for the first year after a transient ischemic attack or stroke, when the risk of recurrent stroke is highest. The use of ticlopidine should be considered on an individual basis in women and men at high risk for noncardioembolic ischemic stroke, especially those with a recent transient ischemic attack or completed stroke. In addition, ticlopidine use is indicated in persons who are intolerant to aspirin or who have recurrence of cerebral ischemia while on aspirin prophylaxis.

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REFERENCES

Gachet C, Savi P, Ohlmann P, Maffrand JP, Jakobs KH, Cazenave JP: ADP receptor induced activation of guanine nucleotide binding proteins in rat platelet membranes—An effect selectively blocked by the thienopyridine clopidogrel. Thromb Haemost 1992; 68:79-83

Gent M, Blakely JA, Easton JD, et al: The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. Lancet 1989; 1:1215-1220

Hass WK, Easton JD, Adams HP Jr, et al: A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients—Ticlopidine Aspirin Stroke Study Group. N Engl J Med 1989; 321:501-507

Pryse-Phillips W for the Ticlopidine Aspirin Stroke Study Group: Ticlopidine Aspirin Stroke Study: Outcome by vascular distribution of the qualifying event. J Stroke Cerebrovasc Dis 1993; 3:49-56

Weisberg LA: The efficacy and safety of ticlopidine and aspirin in nonwhites: Analysis of a patient subgroup from the Ticlopidine Aspirin Stroke Study. Neurology 1993; 43:27-31

Magnetic Resonance Spectroscopy

MAGNETIC RESONANCE SPECTROSCOPY (MRS), a noninvasive method to measure metabolites in brain tissues, has been used to study the abnormalities of stroke, multiple sclerosis, dementia, and encephalopathy.

The basis of nuclear magnetic resonance spectroscopy is that certain atomic nuclei have weak magnetic moments that align in the direction of a strong magnetic field. These nuclei can be manipulated in the magnet to yield information about their anatomical position or biochemical structure. Hydrogen protons in water have resonance properties that allow them to form images in magnetic resonance imaging (MRI). Hydrogen 1 and phosphorus 31 are the two major nuclei with magnetic

moments that have been used in MRS studies of people. Magnetic resonance spectroscopy using ^{1}H is done with suppression of the large signal from water molecules (about 55 mol per liter) so that the protons in other molecules that are present in lower concentrations (1 mmol per liter or more) can be detected. Using ^{31}P, MRS allows the detection of phosphorus in adenosine triphosphate (ATP), phosphocreatine, and membrane phospholipids. It has been used to measure energy substrates, ATP and phosphocreatine, and pH in muscle diseases. One of the first applications of MRS to a human disease, McArdle's disease, a muscle disorder with a metabolic defect in glycogen metabolism, failed to show a normal fall in pH due to lactate accumulation during exercise. Subsequent studies with ^{31}P-MRS have shown abnormalities in pH and metabolites in a number of muscle disorders.

The first application of MRS to the study of brain tissue in humans was also done with ^{31}P-MRS. Infants with anoxic encephalopathy were shown to have decreased energy substrates, which correlated with the extent of injury. Studies in patients with stroke have shown an initial acidosis due to the build-up of lactate and other proton donors in the ischemic tissue. After several days, however, there is tissue alkalosis. This flip-flop of acidosis to alkalosis has been recorded with ^{31}P-MRS and the degree of alkalosis shown to relate to the severity of the infarct. Energy substrates are depleted in the infarcted tissue, but the loss of ATP is a late event, indicating irreversible death of the cells.

Proton MRS has shown early biochemical changes in infarcted brain tissue. The proton spectrum has a large peak from *N*-acetylaspartate, which is mainly found in neurons. The *N*-acetylaspartate signal is preserved early in infarction. It then begins to fall, suggesting that there is a window when cells remain viable and amenable to treatment. Lactate appears in the ^{1}H-MRS spectrum during the acute phase of an infarct.

Other diseases have begun to be studied with MRS. In Alzheimer's disease, a defect in membrane phospholipids has been shown by ^{31}P-MRS. Multiple sclerosis plaques have been shown by ^{1}H-MRS to have a loss of *N*-acetylaspartate in the chronic stage and an increase in lipid signals and choline in the acute stage. Hepatic encephalopathy produces changes in ^{1}H-MRS spectra in the glutamine or glutamate region. Epileptogenic foci have been localized with ^{31}P-MRS.

Magnetic resonance spectroscopy can be done as part of a routine MRI on commercially available MRI instruments in less than an hour. Although it provides unique biochemical information on brain metabolites and is useful in assessing the extent of tissue injury, further studies will be needed to determine its role in diagnosing and planning treatment in neurologic diseases.

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REFERENCES

Arnold DL, Matthews PM, Francis GS, O'Connor J, Antel JP: Proton magnetic resonance spectroscopic imaging for metabolic characterization of demyelinating plaques. Ann Neurol 1992; 31:235-241

Ford CC, Griffey R, Matwiyoff NA, Rosenberg GA: Multivoxel ^{1}H-MRS of stroke. Neurology 1992; 42:1408-1412

Laxer KD, Hubesch B, Sappey-Marinier D, Weiner MW: Increased pH and inorganic phosphate in temporal seizure foci demonstrated by ^{31}P-MRS. Epilepsia 1992; 33:618-623

Levine SR, Helpern JA, Welch KM, et al: Human focal cerebral ischemia: Evaluation of brain pH and energy metabolism with P-31 NMR spectroscopy. Radiology 1992; 185:537-544

Outcomes Research—Possible Effects on Clinical Practice

OVER THE PAST TWO DECADES, there has been a great expansion in neuroscientific knowledge and techniques that are expected to improve the health of patients with neurologic disease. This research has focused on the molecular basis of disease and is expected to result in new therapies, such as transplantation, growth factors, and gene therapies. Expectations are high for the eventual incorporation of the fruits of this research into the clinical practice of neurology.

Along with these advances, growing concern about escalating health care costs has stimulated research into how to identify health care practices that are most cost-effective yet most efficient. Although randomized controlled trials provide the most rigorous data on efficacy—benefit under the best possible circumstances—evidence of efficacy does not necessarily mean that a procedure or treatment will be effective outside the trial setting. The high cost and time requirements of randomized controlled trials also prevent using them for evaluating a large number of treatments or procedures. Finally, results of these trials may not be generalizable to many patients because of exclusion criteria for the trials.

A proposed method for addressing this problem is "outcomes research," so called because of its emphasis on measuring clinically relevant health outcomes. These include not only disease symptoms and mortality, but also daily functioning and activities, emotional well-being, and other dimensions of health-related quality of life. Other features of outcomes research are the use of observational studies, that is, data collected from nonexperimental studies, with careful adjustment for case mix and other possible confounding variables; the use of relatively large data bases (some have advocated that all patient visits be entered into a data base to evaluate outcomes); the use of quantitative techniques to analyze the existing medical literature; and the incorporation of patient preferences for different health outcomes in making clinical decisions. To date, two large-scale federally funded outcome studies have been undertaken to evaluate neurologically relevant conditions: low back pain and stroke prevention. A smaller outcome study of epilepsy surgery and an effort to develop clinical guidelines for rehabilitation after stroke using quantitative literature review and expert panel consensus are also in progress.

What are the mechanisms by which this growth in outcomes research may affect the clinical practice of neurology (and other specialties)? The first is by educating practicing physicians. This can be accomplished through the journal publication of meta-analyses and